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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,664	08/17/2001	Denise L. Faustman	DLF-002.1P	4530

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EXAMINER

AFREMOVA, VERA

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicati n No.

09/913,664

Applicant(s)

FAUSTMAN, DENISE L.

Examiner

Vera Afremova

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 October 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 and 16-23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-14 and 16-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

DETAILED ACTION

In view of the Appeal brief filed on 10/28/2004, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

- (1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,
- (2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

Status of claims

Pending claims 1-14 and 16-23 (amendment filed 6/25/2003) are under examination in the instant office action.

Claims 15 and 24-37 were canceled by applicant. [Paper No. 11 filed 6/25/2003].

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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Claims 1, 2 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,081,030.

Claims are directed to a method for inhibiting rejection by a host mammal of another mammal donor tissue wherein the method comprises step of treating a viable donor tissue with an enzyme effective for removing MHC Class I antigen, step of transplanting the treated viable donor tissue into host mammal before MHC are re-expressed and step maintaining the treated viable donor tissue in the host mammal. Some claims are further drawn to donor and host mammals belonging to the same species. Some claims are further drawn to the use of tissue cells such as blood cells, precursor cell, bone marrow cells.

US 5,081,030 discloses a method for transplantation bone marrow cells wherein the method comprises step of treating a viable donor tissue with enzyme chymopapain (col.11, lines 30-35), step of transplanting the treated viable donor tissue into host mammal (col.11, line 45) and step maintaining the treated viable donor tissue in the host mammal (col. 11, line 57). The cited patent clearly teaches that cells retain viability after enzymatic treatment. Both donor and host are rats or mammals belonging to the same species. The cited patent teaches that enzymatic treatment is intended to release cell surface molecules and that proteases including chymopapain and papain release cell surface proteins and glycoprotein antigens. The cited patent is considered to anticipate the claimed invention because it comprises identical active steps and, thus, the intended effects are reasonably expected to be identical as related to removal of antigens of MHC class I and to inhibition of donor tissue rejection, particularly in view that the cited patent demonstrates better survival of animals received engraftment of enzymatically treated cells.

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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12-14 and 16-23
Claims 1-9, ~~and 12-23~~ are rejected under 35 U.S.C. 103(a) as being unpatentable over US

5,081,030 taken with Galati et al. (IDS reference; Cytometry. 1997, 27: 77-83); US 6,617,171; US 5,670,358 and US 6,156,306.

Claims are directed to a method for inhibiting rejection by a host mammal of a donor tissue transplant derived from another mammal wherein the method comprises step of treating a viable donor tissue with an enzyme effective for removing MHC Class I antigen and steps of transplanting and maintaining the treated viable tissue into/in the host mammal. Some claims are/are further drawn to the second transplanting step in the method for inhibiting transplant rejection. Some claims are further drawn to donor and host mammals belonging to the same or different species. Some claims are further drawn to host mammal being human. Some claims are further drawn to the use of tissues cells and/or organ parts such as blood cells, precursor cell, bone marrow cells, liver, brain, pancreas, kidney, etc. Some claims are further drawn to the use of enzyme papain and to the use of specific time and concentration for papain treatment of the donor tissue in the method for inhibiting transplant rejection.

US 5,081,030 (Civin) teaches a method for transplantation of donor tissue cells that are enzymatically treated in order to remove surface molecules or glycoprotein antigens and it demonstrates better survival of host animals that received engraftment of the enzymatically

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treated donor tissue cells. The disclosure relates to graft vs. host disease (GVHD) and, thus, to inhibition of rejection of donor tissue by host recipient (col. 1, lines 26-33) as encompassed by the presently claimed invention. The cited patent demonstrates that increase of grafting cell doses result in better survival of engraftment recipients and, thus, US 5,081,030 suggests transplantation of additional or second donor tissues as encompassed by the present invention (claim 12). US 5,081,030 also teaches that release of various antigenic cell surface molecules is achieved with proteases and glycosidase (col. 4, lines 58- 68).

In particular example, the cited patent US 5,081,030 (Civin) describes chymopapain enzymatic treatment of donor tissue before transplantation into host. However, it further teaches and suggests enzymatic treatment with proteases including chymopapain and papain in order to release cell surface proteins and glycoprotein antigens (col. 5, line 2). Although the cited patent US 5,081,030 is silent that the enzymatically removed glycoprotein antigens are MHC class I antigens, the enzymes that are used in the method of US 5,081,030 including papain remove MHC class I antigens as adequately demonstrated by Galati et al for papain (see abstract). Furthermore, US 6,617,171 also teaches the method of treating tissues to render them suitable for transplant by incubating with enzymes capable of cleaving MHC class I antigens. The useful enzymes capable to remove MHC class I include endoproteinase, pepsin, papain, chymotrypsin, trypsin, collagenase, etc. with papain being particularly of use (col. 37, lines 52-65 and col. 38, lines 53-65).

In particular example, the cited patent US 5,081,030 (Civin) describes enzymatic treatment of donor bone marrow tissue cells before transplantation into host. However, it also teaches and suggests a variety of cells that would be suitable for enzymatic treatment and

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transplantation including bone marrow, lymphocytes and hormone-secreting cells (col. 4, lines 8-10) and, thus, it suggests enzymatic treatment of tissue cells derived from various organs or organ part including pancreas, liver, kidney, brain, etc as encompassed by the claimed invention. In addition, US 5,670,358 is relied upon to demonstrate that hepatocytes and islets cells useful for transplantation are prepared by enzymatic treatment with chymopapain or papain (abstract).

The cited US 5,081,030 (Civin) teaches and demonstrates better survival of host animals that received engraftment of the enzymatically treated viable donor tissue cells but it is silent about re-expression of MHC class I antigens. However, US 6,156,306 demonstrates that cells treated with papain in order to remove MHC class I surface molecules will further re-express the MHC class I surface molecules (col. 16, lines 10-17).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to practice the presently claimed invention drawn to transplantation of viable donor tissues treated with enzymes capable to remove antigenic glycoproteins belonging to MHC class I as it is taught and suggested by US 5,081, 030 with a reasonable expectation of success in inhibiting rejection by host mammal of donor tissue and improving host survival as demonstrated by US 5,081, 030 because enzymes used and suggested in the method of US 5,081, 030 are capable to remove antigenic surface molecules including antigenic glycoprotein MHC class I as adequately demonstrated and taught by Galati et al., US 6,617,171 and US 6,156,306. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary. It is considered to be within the purview of one of ordinary skill in the art to adjust time and concentration of enzymes including papain for treating donor tissues and for removal of antigenic molecules.

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The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Claims 1-14 and 16-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,081,030 taken with Galati et al. (IDS reference; Cytometry. 1997, 27: 77-83); US 6,617,171; US 5,670,358 and US 6,156,306 as applied to claims 1-9 and ^{12-14 and 16-23}~~12-23~~ above, and further in view of Stone et al. (IDS reference; Transplantation. 1998. 65 (12) : 1577-1583).

Claims 1-9 and ^{12-14 and 16-23}~~12-23~~ as explained above. Claims 10 and 11 are further drawn to the use of combination of papain and alpha-galactosidase in the method for inhibiting transplant rejection.

US 5,081,030 taken with Galati et al. (IDS reference; Cytometry. 1997, 27: 77-83); US 6,617,171; US 5,670,358 and US 6,156,306 are relied upon as explained above.

In particular example, the cited patent US 5,081,030 (Civin) describes enzymatic treatment of donor tissue with one enzyme. However, it also teaches that release of various antigenic cell surface molecules is achieved with proteases and glycosidase (col. 4, lines 58- 68). Glycosidase such as or alpha-galactosidase is known to remove alpha-gal epitopes from xenografts and, thereby to alter immune response of host recipient.

For example: the reference by Stone et al. demonstrates that transplantation of xenografts treated with or alpha-galactosidase reduced inflammatory response of recipients (see abstract). The reference by Stone et al. [IDS-BJ] discloses a method for inhibiting transplant wherein the method comprises step of treating donor tissue with galactosidase and step of transplanting the treated tissue in to host recipient and wherein the method results in a reduction of inflammatory

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reaction or immune response of recipient host (pages 1577-1578 at paragraphs "Methods" and "Conclusions").

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was to combine papain and alpha-galactosidase for removal of antigenic and/or inflammatory cell surface molecules in the method for graft transplantations as suggested for generic protease and glycosidase by US 5,081,030 with a reasonable expectation of success in inhibiting rejection and reducing inflammatory host response because papain and alpha-galactosidase have been known and used in the prior art method for graft preparation and transplantation as adequately demonstrated by all cited references combined with Stone et al. One of skill in the art would have been motivated to combine two types of enzymes protease and glycosidase for the expected benefit in removing variety of cell surface antigenic structures as suggested by US 5,081,030. One of skill in the art would have been motivated to combine papain and galactosidase for the expected benefit in removing various surface antigenic structures because papain and alpha-galactosidase are taught and suggested as particularly useful enzymes for removal of antigenic cell surface structures that are MHC class I glycoproteins and that are gal-epitopes respectively. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicant's arguments filed 10/28/2004 been fully considered but are moot in view of the new ground(s) of rejection.

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Claim rejections over US 4,399,123 and US 5,397,353 have been withdrawn because methods of graft transplantation disclosed by these patents encompass the use of non-viable graft tissues. The graft tissues are non-viable because they are substantially free or free of all cellular elements and, therefore, the graft tissues do not contain cells or living cells. For example: see US 4,399,123 at col. 1, line 59-61. See US 5,397,353 at col. 3, lines 15-24 and 39-41.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Vera Afremova

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January 7, 2005



VERA AFREMOVA

PATENT EXAMINER



Michael G. Wityshyn
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